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ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/522,370	STANGL ET AL.	
	Examiner	Art Unit	
	RONALD T. NIEBAUER	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-14,16-23,25 and 26* is/are pending in the application.

4a) Of the above claim(s) *19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-14,16-18,20-21,23,25-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants amendments and arguments filed 12/28/07 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn.

As noted previously applicant elected the following species with traverse:

disease type – cardiac;

fibrosis cause – pressure stress in arterial hypertension;

proteasome inhibitor – threonine protease inhibitor MG132.

The procedure for examination of Markush type claims is highlighted in MPEP section 803.02:

> Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability. If the Markush-type claim is not allowable, the provisional election will be given effect and examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration.
>
> The examination will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action can be made final unless the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p).

In the instant case, each of the elected species were found in the prior art (see rejections below). In the course of searching for the elected species any art that was uncovered that reads on a non-elected species is also cited herein.

It is noted that applicant elected cardiac as the disease type. Claim 19 is drawn to organs other than the heart and as such does not read on the elected species.

Claim 19 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 4/25/07.

Claims 1-10,15,22,24 have been cancelled. Claims 11,14,21,23,26 have been amended.

Claims 11-14,16-18,20-21,23,25-26 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 is drawn to a method of treating cardiac fibrosis of a patient in need thereof where the fibrosis is mediated by the renin-angiotensin-system. It is unclear if the recitation of 'mediated by the renin-angiotensin-system' is meant to define the patient population. If so, it is unclear how to identify such a patient population (i.e. a patient in need thereof). It is noted that page 1 lines 20-27 of the instant specification discuss rennin-angiotensin but such a discussion does not clearly set forth how to identify such a patient population. Further, it is noted that claim 14 recites that cardiac fibrosis is mediated. Since mediate means to reconcile or settle, it is unclear why the patient population would need the treatment if the fibrosis has been mediated.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-14,16-18,20-21,23,25-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*,

> 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus …") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the

claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, the claims are drawn to a method of treatment using proteasome inhibitors. The inhibitors are described as organic compounds with a relative molar mass less than or equal to 1000 (claim 21); N-terminal threonine protease inhibitors (claim 21); peptide aldehydes (claim 21); peptide boronates (claim 21); binding peptide/protein directed against ubiquitin and/or against the proteasome (claim 23); nucleic acid directed against at least one component of the proteasomal system (claim 25); an antibody or antigen binding part (claim 25); an anti-sense RNA against a proteasome encoding sequence (claim 26); a knock-out construct against a proteasome encoding sequence (claim 26), for example.

(1) Level of skill and knowledge in the art:

The level of skill in the art is high.

(2) Partial structure:

The proteasome inhibitors are described for example as organic compounds with a relative molar mass less than or equal to 1000 (claim 21); N-terminal threonine protease inhibitors (claim 21); peptide aldehydes (claim 21); peptide boronates (claim 21); binding peptide/protein directed against ubiquitin and/or against the proteasome (claim 23); nucleic acid directed against at least one component of the proteasomal system (claim 25); an antibody or antigen binding part (claim 25); an anti-sense RNA against a proteasome encoding sequence (claim 26); a knock-out construct against a proteasome encoding sequence (claim 26).

In considering the possible variability of the genus it is noted that there are many possible organic compounds with molar mass less than or equal to 1000. There are many possible peptide aldehydes. There are many possible binding peptide/protein directed against ubiquitin and/or against the proteasome. There are many possible nucleic acid directed against at least one component of the proteasomal system. There are many possible antibody or antigen binding part.

There are many possible anti-sense RNA against a proteasome encoding sequence. There are many possible knock-out construct against a proteasome encoding sequence.

Hence, there is substantial variability in the genus. The genus includes a wide variety of molecules including organic compounds, peptides, nucleic acids, and knock-out constructs.

The claims (claim 26 for example) recite several specific molecules such as MG132, PSI, and ALLN. The specification also provides examples on page 3 (the first complete paragraph). Since there are a substantial variety of molecules possible within the genus, the examples do not constitute a representative number of species and do not sufficiently describe the genus claimed (see Gostelli above). For example, there are no specific examples of nucleic acid sequences directed against the proteasomal system. Of the many possible peptides there are only 5 SEQ IDs on record in the application.

(3) Physical and/or chemical properties and (4) Functional characteristics:

The claims are drawn to proteasomal inhibitors. However, there is no known or disclosed correlation between structure and function. Further, peptides are described as being directed against ubiquitin and/or against the proteasome; nucleic acids are described as being directed against at least one component of the proteasomal system; knock-out constructs are described as being directed against a proteasome encoding sequence. However, there is no known or disclosed correlation between structure and function. In particular, no common sequence or common core is taught for the proteasomal inhibitors.

(5) Method of making the claimed invention:

The specification (page 6 line 18) describes that 3 selected inhibitors were purchased.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that the claim(s) is/are broad and generic, with respect to all possible molecules encompassed by the claims. The possible structural variations are many. Although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the molecules beyond those molecules specifically disclosed in the examples in the specification. Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus. While having written description of moilecules identified in the specification tables and/or examples, the specification does not provide sufficient descriptive support for the myriad of molecules embraced by the claims.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Response to Arguments

It is noted that the current rejection is maintained in part from the previous rejection. The arguments are considered and addressed to the extent that they apply to the current rejection.

In the arguments filed 12/28/07 applicants argue that it is routine in the art to make antibodies or antigen parts when the targets are known. Applicants argue that antisense and knock out technology was known in the art at the time the present invention was made and one skilled in the art would be able to prepare antisense RNA and knock out constructs.

The arguments have been fully considered but they are not persuasive.

The availability of technology does not adequately describe the myriad of molecules encompassed by the instant claims. In particular, technology to make molecules does not provide specific description of any structural features of the molecules. For example, peptide synthesis is known in the art. However, just because the technology is available does not describe the range and variety of peptides that can be synthesized. As highlighted above 'methods of making' is not the only criteria to consider for determining adequate written description.

Claim Rejections - 35 USC § 102

The 102(e) rejection using Schubert et al., has been withdrawn. In particular, the patient population of Schubert (fibrosis caused by inflammatory response) does not meet the limitations of the instant claims.

The 102(e) rejection using Pluenneke has been withdrawn. In addition to the claim amendments and arguments, it is noted that Pluenneke only disclose the administration of proteasome inhibitors to those with cancer which does not meet the limitations of the instant claims.

The following are new claim rejections:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Takaoka et al. (Current Topics in Pharmacology 2000 v5 pages 99-106).

Takaoka teach the administration of a proteasome inhibitor to mice with hypertension (abstract). Takaoka teach that the proteasome may represent a potent target for cardiovascular diseases and discuss the peptide aldehyde inhibitors calpain inhibitor 1 and MG115 (page 99 2nd column 1st full paragraph). Takaoka teach (figure 1) administration of proteasome inhibitor PSI (identical to SEQ ID NO:1 of the instant invention) a peptide aldehyde (page 102 2nd column first full paragraph) to hypertensive mice at a dose of 3 mg/kg (page 100 1st column 2nd complete paragraph) thus meeting the active step (i.e. administration) and compound (i.e. proteasome inhibitor) of claims 12-14 of the instant invention. Takaoka teach positive results and state that 'PSI treatment clearly ameliorated the structural changes induced by DOCA-salt' (page 101 lines 3-4). Takaoka teach that hypertensive rats have increased wall thickness of aortas (i.e. cardiac fibrosis) (table 1 figure 2) thus the patient population of claims 12-14 of the instant invention are met.

Although unclear (see 112 2nd above) claim 14 has been given its broadest reasonable interpretation (see MPEP section 2111) such that the patient population includes those with cardiac fibrosis.

Claims 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Okamoto et al. (European Journal of Pharmacology 1998, 350:R11-R12) as evidenced by Querejeta et al. (Circulation April 11 2000, 1729-1735).

Okamoto teach the administration of a proteasome inhibitor to mice with hypertension (abstract). Okamoto teach that the proteasome is a target for cardiovascular disease (page R11 column 1). Okomato specifically teach the use of the proteasome inhibitor PSI (see the sentence spanning column 1 and 2 of page R11) which is identical to SEQ ID NO:1 of the instant invention. Okamoto teach the administration of 3mg/kg of PSI to the hypersensitive rats (page R11 column 2).

It is noted that Okamoto does not expressly teach that those who have hypertension necessarily have fibrosis. Querejeta et al. teach that hypertensive subjects have fibrous tissue accumulation and hence fibrosis (see 1st sentence page 1729). As such, Querejeta is cited as evidence that Okamoto meet the limitations of the patient population recited in claims 12-14 for example of the instant invention. It is noted that since Querejeta is cited to show a universal fact, it does not need to be available as prior art (MPEP section 2124). It is also noted that applicants specification (page 1 lines 9-10) teach that myocardial fibrosis is a reaction to overload such as that caused by high blood pressure (i.e. hypertension), consistent with the teaching of Querejeta et al.

Although unclear (see 112 2nd above) claim 14 has been given its broadest reasonable interpretation (see MPEP section 2111) such that the patient population includes those with cardiac fibrosis.

Claims 11-14,16-18,20-21,23,25-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Brand et al. (WO 98/35691) as evidenced by Jain et al. (Am J Physiol Heart Circ Physiol 2002, 283: H2544-2550).

Brand teach a method of lessening the severity of myocardial infarction (claim 9) by administering to a patient an effective amount of a proteasome inhibitor (claims 1-3 for example). Brand teach that the compound can be administered at any time before, during or after the onset of ischemia (page 13 lines 4-5). Brand teach that the effective amounts of the compounds will vary between about 10ug and about 50mg per kg of body weight (page 12 lines 30-32). Brand specifically teach the use of 0.1 mg/kg of a proteasome inhibitor (page 15 line 15) in one of the examples thus meeting the dosages recited in claims 11,16,17 of the instant invention. Brand teach a variety of suitable proteasome inhibitors (claims 12-16 page 11 line 26-page 12 line 26 for example) including peptide aldehyde (page 4 line 12, page 11 line 28, claim 12) thus meeting the limitations of claims 21,25; peptide inhibitors directly against the proteasome (page 11 line 26-30 for example) thus meeting the limitations of claim 23 of the instant invention; inhibitors such as lactacystin (page 4 line 13, page 12 line 17 for example) thus meeting the limitation recited in claim 26 of the instant invention. Since the treatment is toward myocardial infarction (claim 9) and heart attacks are mentioned in the specification (page 1 line 21-22) the disease is related to organs (i.e. the heart) and the cardiovascular thus meeting the limitations of claims 18,20 of the instant invention.

It is noted that Brand does not expressly teach that those who have experienced myocardial infarction necessarily have fibrosis. Jain et al. teach that after myocardial infarction

there is an increase in interstitial fibrosis (page H2544 first sentence). Therefore those who have experienced myocardial infarction necessarily have fibrosis. As such, Jain is cited as evidence that Brand meet the limitations of the patient population recited in claims 11-14 for example of the instant invention. It is noted that since Jain is cited to show a universal fact, it does not need to be available as prior art (MPEP section 2124). It is also noted that applicants specification (page 1 lines 9-10) teach that myocardial fibrosis is a reaction to overload such as that caused by myocardial infarction, consistent with the teaching of Jain et al.

Although unclear (see 112 2nd above) claim 14 has been given its broadest reasonable interpretation (see MPEP section 2111) such that the patient population includes those with cardiac fibrosis.

Claim Rejections - 35 USC § 103

The previous 103 rejection using Pluenneke has been withdrawn. In addition to the claim amendments and arguments, it is noted that Pluenneke only disclose the administration of proteasome inhibitors to those with cancer which does not meet the limitations of the instant claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11,16-18,20-21,23,25,26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takaoka et al. (Current Topics in Pharmacology 2000 v5 pages 99-106) as applied to claims 12-14 above, and further in view of Takaoka et al. (Current Topics in Pharmacology 2000 v5 pages 99-106) (the same reference).

As discussed above Takaoka teach the administration of a proteasome inhibitor to mice with hypertension (abstract). Takaoka teach that the proteasome may represent a potent target for cardiovascular diseases and discuss the peptide aldehyde inhibitors calpain inhibitor 1 and MG115 (page 99 2nd column 1st full paragraph). Takaoka teach (figure 1) administration of proteasome inhibitor PSI (identical to SEQ ID NO:1 of the instant invention) a peptide aldehyde (page 102 2nd column first full paragraph) to hypertensive mice at a dose of 3 mg/kg (page 100 1st column 2nd complete paragraph) thus meeting the active step (i.e. administration) and compound (i.e. proteasome inhibitor) of claims 12-14 of the instant invention. Takaoka teach positive results and state that 'PSI treatment clearly ameliorated the structural changes induced by DOCA-salt' (page 101 lines 3-4). Takaoka teach that hypertensive rats have increased wall

thickness of aortas (i.e. cardiac fibrosis) (table 1 figure 2) thus the patient population of claims 12-14 of the instant invention are met.

Takaoka does not expressly teach the doses recited in claim 11 for the treatment of fibrotic diseases such as hypertension.

Takaoka teach (figure 1) administration of the proteasome inhibitor PSI (identical to SEQ ID NO:1 of the instant invention) a peptide aldehyde (page 102 2nd column first full paragraph) to hypertensive mice at a dose of 3 mg/kg (page 100 1st column 2nd complete paragraph). In a related ischemia model Takaoka teach PSI administration at 0.1 mg/kg (table 2) and teach that the improvements after the treatment with PSI must result from the inhibition of the proteasome (page 104 1st paragraph).

Since Takaoka teach positive results and state that 'PSI treatment clearly ameliorated the structural changes induced by DOCA-salt' (page 101 lines 3-4) one would be motivated to determine all optimum and operable conditions. Since Takaoka teach variable doses for a related ischemia model, in particular 0.1 mg/kg of PSI (table 2), one would be motivated to use that dose in the hypertensive model. Further, Takaoka also teach 0.1 mg/kg doses for the proteasome inhibitor lactacystin (page 105 1st column last paragraph).

It would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g. dosing amounts), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine

experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). *See* MPEP § 2145.05).

As such one would be motivated to try a 0.1 mg/kg dose of PSI for the hypertension model thus meeting the limitations of claims 11,16-17 of the instant invention. Takaoka expressly teach treatment for hypertension (abstract) and relates the effects to other cardiovascular diseases (page 101 last paragraph) thus meeting the limitations of claims 18,20 of the instant invention. Takaoka expressly teach the proteaseome inhibitor PSI a peptide aldehyde (figure 1, page 102 2nd column first full paragraph) thus meeting the limitations of claims 21,23,25-26 of the instant invention.

Although unclear (see 112 2nd above) claim 14 has been given its broadest reasonable interpretation (see MPEP section 2111) such that the patient population includes those with cardiac fibrosis.

Claims 11,16-18,20-21,23,25,26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takaoka et al. (Current Topics in Pharmacology 2000 v5 pages 99-106) as applied to claims 12-14 above, and further in view of Takaoka et al. (Current Topics in Pharmacology 2000 v5 pages 99-106) (the same reference) and Elliot et al. (AJCP 2001 116:637-646).

As discussed above Takaoka render claims 11,16-18,20-21,23,25,26 unpatentable.

Takaoka does not expressly teach the elected species of proteasome inhibitor MG132.

Takaoka expressly teach the proteasome inhibitor PSI a peptide aldehyde (figure 1, page 102 2nd column first full paragraph). Takaoka also teach the importance of related peptide aldehyde inhibitors including MG115 and calpain inhibitor 1 (page 99 2nd column first full paragraph) and lactacystin (page 105 1st column last paragraph) and generally teach the use of proteasome inhibitors (page 105 last paragraph). Since Takaoka teach the use of proteasome inhibitors in general and specifically peptide aldehyde inhibitors with successful results one would be motivated to substitute various peptide aldehyde proteasome inhibitors.

Elliot teach (abstract, page 641 column 2) proteasome inhibitors for treatment after myocardial infarction. Elliot teach (Table 1) MG132 as a specific peptide aldehyde and teach that MG132 has high potency (page 638 2nd column 2nd complete paragraph). Since Elliot teach that MG132 has high potency one would be motivated to substitute MG132 into the method of Takaoka. Such a method reads on the elected species of the instant invention as recited in claim 26 of the instant invention for example.

It has been recently held that "Neither §103's enactment nor *Graham*'s analysis disturbed the Court's earlier instructions concerning the need for caution in granting a patent based on the combination of elements found in the prior art." KSR v. Teleflex, 550 U.S. ___, 82 USPQ2d 1385, 1389 (2007). The KSR court stated that "a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." KSR at 1389.

Furthermore, The KSR court concluded that "obvious to try" may be an appropriate test under 103. The Supreme Court stated in *KSR*

> When there is motivation
>
> "to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical

> grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, ___, 82 USPQ2d 1385, 1397 (2007).

In the instant case the claim would have been obvious because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art in the art at the time of the invention.

Although unclear (see 112 2nd above) claim 14 has been given its broadest reasonable interpretation (see MPEP section 2111) such that the patient population includes those with cardiac fibrosis.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11-14,16-21,23,25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1,3-9,27-30 of copending Application No. 10/522,706 ('706) and Jain et al. (Am J Physiol Heart Circ Physiol 2002, 283: H2544-2550).

'706 teach the administration of proteasome inhibitors such as MG132 (claim 1,30) to a patient in need thereof including those with heart failure and myocardial infarction (claims 4-5). Jain et al. teach that after myocardial infarction there an increase in interstitial fibrosis (page H2544 first sentence). Therefore those who have experienced myocardial infarction necessarily have fibrosis. As such, Jain is cited as evidence that '706 teach the patient population of claims 11-14,16-21,23,25 of the instant invention. Since '706 teach MG132 and a wide range of other proteaseome inhibitors the proteasome inhibitor limitations of claims 11-14,16-21,23,25 of the instant invention are met. Although '706 do not expressly recite doses it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g. dosing amounts), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). *See* MPEP § 2145.05).

Although unclear (see 112 2nd above) claim 14 has been given its broadest reasonable interpretation (see MPEP section 2111) such that the patient population includes those with cardiac fibrosis.

This is a provisional obviousness-type double patenting rejection.

Claims 11-14,16-21,23,25 are directed to an invention not patentably distinct from claims 1,3-9,27-30 of commonly assigned 10/522,706 as discussed above

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned 10/522,706, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RONALD T. NIEBAUER whose telephone number is (571)270-3059. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, alt. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ronald T Niebauer/
Examiner, Art Unit 1654

/Anish Gupta/

Primary Examiner, Art Unit 1654